Arterial stiffness and pulse pressure in CKD and ESRD

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We recognize that increased systolic pressure is the most challenging form of hypertension today and that pulse pressure as an independent cardiovascular risk factor has focused attention on arterial stiffness and wave reflections as the most important factors determining these pressures. In recent years, many studies emphasized the role of arterial rigidity in the development of cardiovascular diseases, and it was shown that stiffening of arteries is associated with increased cardiovascular mortality and morbidity. Moreover, arterial stiffening is linked to decreased glomerular filtration rate, and is predictive of kidney disease progression and the patient's cardiovascular outcome. Premature vascular aging and arterial stiffening are observed with progression of chronic kidney disease (CKD) and in end-stage renal disease (ESRD). This accelerated aging is associated with outward remodeling of large vessels, characterized by increased arterial radius not totally compensated for by artery wall hypertrophy. Arterial stiffening in CKD and ESRD patients is of multifactorial origin with extensive arterial calcifications representing a major covariate. With aging, the rigidity is more pronounced in the aorta than in peripheral conduit arteries, leading to the disappearance or inversion of the arterial stiffness gradient and less protection of the microcirculation from high-pressure transmission. Various non-pharmacological or pharmacological interventions can modestly slow the progression of arterial stiffness, but arterial stiffness is, in part, pressure dependent and treatments able to stop the process mainly include antihypertensive drugs.

Kidney International (2012) **82,** 388–400; doi:10.1038/ki.2012.131; published online 25 April 2012

KEYWORDS: arterial aging; arterial remodeling; arterial stiffness; chronic kidney disease; end-stage renal disease

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Received 20 September 2011; revised 16 January 2012; accepted 17 January 2012; published online 25 April 2012

Cardiovascular disease is a major cause of morbidity and mortality in patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD). Epidemiological and clinical studies showed that structural and functional changes of central and large conduit arteries are major contributing factors associated with these complications.[1–3] These changes concern the two interrelated arterial functions: delivering adequate blood flow to tissues and organs, as dictated by their metabolic activity (conduit function), and transforming cyclic high-flow and pressure oscillations in the aorta into continuous and low-pressure capillary flow (cushioning or dampening function).[4,5]

Atherosclerosis, characterized by atheromatous plaques with restriction of blood flow and ischemia or infarction of downstream tissues, is the principal long-term alteration of conduit function, and a frequent cause of ischemic heart disease, strokes, and peripheral artery diseases. Dampening function disorders reflect changes of arterial wall viscoelastic properties and dimensions, and are more typically associated with left ventricular hypertrophy, congestive heart failure, and sudden death.[6–12] Results of cross-sectional studies emphasized the role of arterial stiffness as an independent cardiovascular risk factor and predictor of all-cause and cardiovascular death in many populations, as well as of diseases such as coronary atherosclerosis, diabetes, ESRD, aging, coronary events, and stroke.[13–22]

DAMPENING FUNCTION AND ARTERIAL STIFFNESS

The arterial wall has elastic and viscous properties. Their difference reflects the time-dependent response of the stress–strain relationship (arterial pressure–arterial diameter changes). In a purely elastic artery, this relationship is time independent and, after stress removal, the arterial diameter returns to its initial dimensions. In the presence of wall viscosity, the arterial wall retains part of the deformation, meaning that part of the left ventricular energy responsible for strain is dissipated, characterized by hysteresis of the pressure–diameter loop.[23] As it is difficult to measure and evaluate in humans, the role of arterial 'viscosity' has not been evaluated as extensively as the 'elastic' properties of arteries. In contrast, a vast body of literature on elastic properties is available.

Definitions

The ability of arteries to accommodate the stroke volume can be described in terms of compliance or arterial stiffness.[24] These terms express the contained volume of the vasculature (total or segmental), as a function of a given transmural pressure. Compliance (C) describes the absolute volume change (ΔV = strain) due to a pressure change (ΔP = stress): $C = \Delta V/\Delta P$. The reciprocal value of compliance is elastance ($E = \Delta P/\Delta V$) or stiffness. Compliance can be expressed relative to the initial volume (V) as a coefficient of distensibility D_i, defined as $D_i = \Delta V/V \times \Delta P$. In contrast to compliance or elastance/stiffness, which provides information about the 'elasticity' of the artery as a hollow structure, the elastic incremental modulus (E_{inc}, Young's modulus) provides information on the intrinsic elastic properties of the biomaterials constituting the arterial wall independent of vessel geometry. The pressure–volume relationship is non-linear: at low distending pressure the tension is borne by distensible elastin fibers, whereas at a high distending pressure the tension is transferred and borne by less extensible collagen fibers. Thus, the arterial wall gets stiffer and more 'resistant' to distension, limiting arterial blood pooling during left ventricular ejection. The most typical clinical consequence of arterial stiffening is a steep pressure–volume relationship, with increased systolic pressure during ventricular ejection and decreased diastolic pressure during diastolic runoff, resulting in high pulse pressure.[24]

Arterial dampening has two aspects: transformation of cyclic blood flow in the aorta into a continuous capillary flow and dampening of arterial pressure oscillations, thereby limiting their transmission to the microcirculation. The efficiency of these functions depends on the stiffness and geometry of the aorta and central arteries, and rigidity of successive arterial segments (stiffness gradient).[24–26]

Arterial stiffness and resistance to distension

During ventricular contraction, part of the stroke volume is forwarded directly to the peripheral tissues, and part of it is momentarily stored in the aorta and central arteries, stretching the arterial walls and raising local blood pressure. Part of the energy produced by the heart is diverted for the distension of arteries and is 'stored' in the vessel walls. During diastole, the 'stored' energy recoils the aorta, propelling the accumulated blood forward into the peripheral tissues, ensuring continuous flow (Figure 1). To limit the cardiac work required during ventricular ejection, the energy necessary for arterial distension and recoil should be low, i.e., for a given stroke volume, the pressure increase should be as small as possible. The efficiency of this function depends on artery stiffness and geometry. When rigidity is mild, the arterial wall opposes low resistance to distension and the pressure effect is minimized. When the arterial system is rigid and cannot be stretched, the entire stroke volume flows through the arterial system and peripheral tissues only during systole with two consequences: intermittent flow and short capillary transit time, with reduced metabolic exchanges (Figure 1).[24,26]

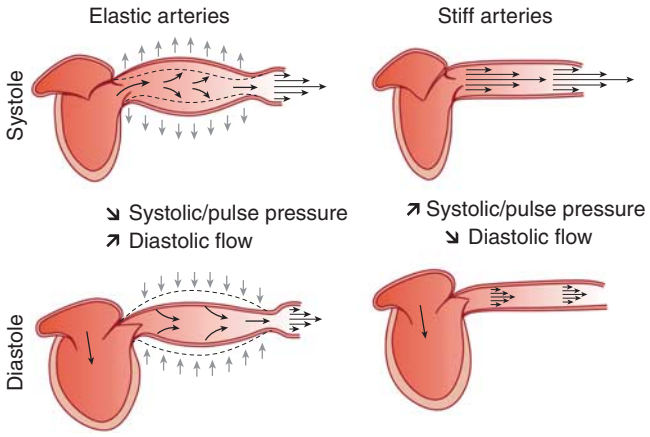

Figure 1 | Schematic representation of the role of arterial stiffness in assuring blood flow through the peripheral circulation.

In addition to influencing the 'resistance to distension', arterial stiffness determines the propagation velocity of the pressure wave from the proximal aorta toward peripheral vessels; i.e., pulse wave velocity (PWV).[4,23,24] The arterial system is heterogenous, with PWV increasing progressively from the ascending aorta to the peripheral muscular conduit arteries, generating a stiffness gradient [25–29] that is important for the regulation of cardiac work and pulsatile pressure transmission to the microcirculation.[25,26,29,30]

PWV is a convenient way to measure arterial stiffness. Briefly, the speed of pressure wave propagation in a solid is proportional to its rigidity. PWV assesses the stiffness of an artery as a hollow structure and according to the Moens and Korteweg's formula: $PWV^2 = E_{inc} \times h/2r \times \rho$. It depends on artery geometry (wall thickness, h; radius, r), intrinsic elastic properties of the arterial wall biomaterials (E_{inc}), and density (ρ).[4,24] PWV must not be confounded with blood velocity. Indeed, although PWV varies between 4 and 5 m/s in the ascending aorta and between 9 and 12 m/s in peripheral conduit arteries,[4,27,28] blood velocity is in the order of cm/s.[5,23,31] PWV represents the transmission of energy through the arterial wall, whereas blood velocity represents the displacement of mass through the incompressible blood column. This difference in speed propagation is physiologically advantageous for left ventricular work and arterial blood flow.

At the start of ventricular ejection, the incompressible blood faces a blood column occupying the aorta and arterial tree. The ejected blood has to find space, which is achieved principally by distending the proximal aorta and propelling the blood column forward. Concomitant to blood entering the aorta, the proximal aortic pressure increase creates a pressure wave with higher proximal pressures than in downstream segments (pressure gradient). All these changes are confined to a short segment of the proximal aorta. These local alterations are transmitted downstream, because the incompressible blood displaced from the proximal aorta must also find its place in downstream segments. The pressure wave moves downstream to distal arterial segments,

rapidly propagating the pressure gradient from segment to segment, i.e., displacing blood downstream. The PWV increase from the aorta to the peripheral arteries quickly propelling the pressure gradient along the arterial tree, resulting in a rapid (in milliseconds) downstream mobilization of blood in the arterial system. This transmission occurs during ventricular ejection, and the downstream displacement of arterial blood 'frees up' space for the stroke volume. Relying only on the 'thrusting' force of blood entering the proximal aorta, the movement of all arterial blood would require very high cardiac energy expenditure to counter the high inertial forces of the blood column. At the end of ventricular ejection, the stroke volume is now occupying the blood column whose length (stroke distance) is measured in centimeters, i.e., mean blood velocity in cm/s.[31] The fact that PWV largely exceeds blood velocity in the aorta is important; otherwise, peak aortic flow velocity exceeding PWV would create conditions for the generation of longitudinal shock waves (similar to those generated by an airplane passing the speed of sound), potentially provoking arterial injury.

Reflected waves and central blood pressure

The arterial stiffness gradient regulates pressure transmission along the arterial tree and to the microcirculation. The arterial pressure wave generated in the aorta (forward or incident wave) is propagated to arteries throughout the body. The stiffness gradient, together with aortic geometry changes (tapering), local arterial branchings, and lumen-narrowing, creates an impedance mismatch, causing partial reflections of forward pressure waves traveling back to the central aorta (reflected waves).[24,32–34] Wave reflections considerably influence the pressure wave amplitude and shape along the arterial tree.[32–35] Forward and reflected pressure waves overlap, and the final amplitude and shape of the pulse pressure wave are determined by the phase relationship (timing) between these component waves.

The overlap between the two waves depends on the site of pressure recording along the arterial tree. Peripheral arteries are close to reflection sites, and the reflected wave occurs at the impact of forward wave, i.e., the waves are in phase producing an additive effect. The ascending aorta and central arteries are distant from reflecting sites, and the return of the reflected wave is variably delayed (*T*sh, time to shoulder) (Figure 2), depending on PWV and traveling distances.[36] In the aorta or central arteries, forward and reflected waves are not in phase. In subjects with low PWV, reflected waves impact on central arteries during end-systole and diastole, increasing the aortic pressure in early diastole but not during systole.[24,32–35] This situation is physiologically advantageous, as the higher diastolic pressure boosts coronary perfusion without increasing the left ventricular pressure load.

This difference in the overlap between component pressure waves in the aorta and peripheral arteries results in lower aortic systolic and pulse pressures, compared with peripheral arteries (central-to-peripheral systolic and pulse pressure amplification) [33–36] (Figure 2). The higher peripheral pressure is also due to the higher peripheral artery stiffness, i.e., the higher local pressure effect of the displaced blood column.

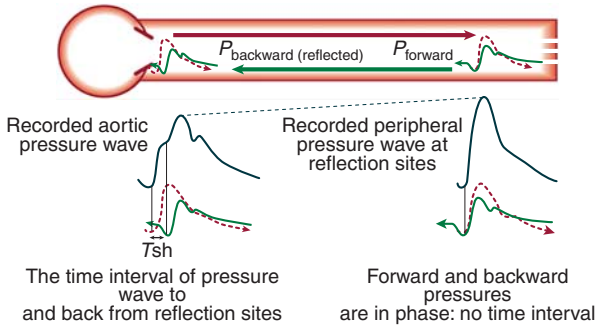

Figure 2 | Representation of forward and reflected pressure wave travel and the influence of their timing and overlap on recorded aortic and peripheral pressure waves. *T*sh, time to shoulder.

Arterial stiffening disrupts the desirable timing. With increased PWV, the reflected waves return earlier, thus impacting the central arteries during systole rather than diastole, amplifying aortic and ventricular pressures during systole, and reducing aortic pressure during diastole. With arterial stiffening (high PWV), the forward and reflected waves in the aorta are almost in phase, and central aortic pressure is close to the peripheral pressure, and the central-to-peripheral systolic and pulse pressure amplification tends to disappear or be attenuated.[4,23,35,36] By favoring early wave reflections, arterial rigidity increases peak- and end-systolic pressures in the ascending aorta, thereby raising myocardial pressure load (left ventricular hypertrophy) and oxygen consumption, and decreasing diastolic blood pressure and subendocardial blood flow.[6–11,34–38]

Influence of age

Young subjects are characterized by significantly lower aortic stiffness than peripheral stiffness, and thus by a significant 'stiffness gradient'[4,24,27,28] (Figure 3a). Partial pressure wave reflections are generated at the transition between these segments, limiting pulsatile energy transmission downstream to the microcirculation.[25,29,30] In young subjects, this process is coupled with low aortic PWV and the reflected wave still returning during diastole. With aging and pathologies, aortic rigidity increases much more than hardening in peripheral arteries, progressively dissipating the stiffness gradient[25,27,28,39] (Figure 3b). The reflection sites are now closer to the microcirculation, increasing pulsatile energy transmission into the peripheral microcirculation.[25,29,30] The arteriolar network is a major site of resistance and reflections, and the ultimate microcirculation protection against pulsatile pressure transmission.[4,24,34]

This protection is highly dependent on an intact myogenic response and autoregulatory response, characterized by vasoconstriction, increased vascular resistance, and, in the

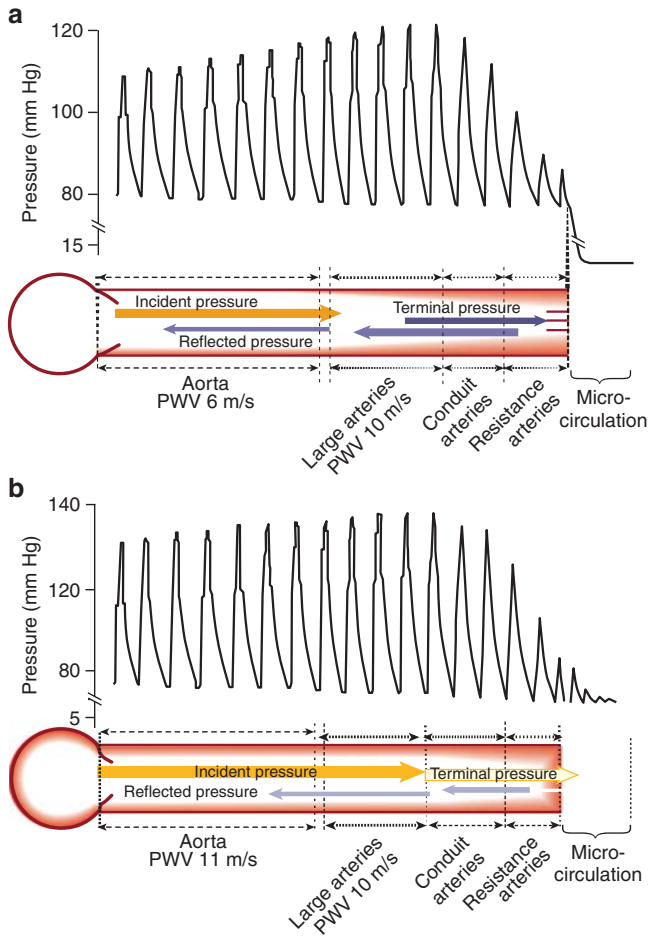

Figure 3 | Stiffness gradient. (**a**) When an arterial stiffness gradient is present (aortic pulse wave velocity (PWV) < peripheral PWV), partial reflections occur far from the microcirculation and return at low PWV to the aorta in diastole, thereby maintaining central-to-peripheral amplification. Partial reflections limit the transmission of pulsatile pressure energy to the periphery and protect the microcirculation. (**b**) When the stiffness gradient disappears or is inverted (aortic PWV > peripheral PWV), pulsatile pressure is not sufficiently dampened and is transmitted, damaging the microcirculation. In parallel, the central-to-peripheral pressure amplification is attenuated.

long term, lead to structural inward microvessel remodeling.[40,41] Autoregulation is an important protective mechanism in highly perfused organs with low arteriolar resistance, particularly the brain and kidney.[24,29,30,40] Loss of renal blood flow autoregulation leads to pulsatile energy transmission and higher dissipation in the microcirculation, with consequent hyperfiltration and subsequent glomerulosclerosis, and progressively diminished kidney function,[42] as observed in several conditions, e.g., aging, diabetes, hypertension, and chronic nephropathies.[43–46] The decreased stiffness gradient associated with high aortic PWV and higher pressure transmission to the microcirculation could account for the inverse relationships observed between aortic PWV and impaired kidney (and brain) function.[47–55]

Arterial tensile and shear stresses

Arterial stiffening can be associated with modified E_{inc} (collagen accumulation and cross-links, broken elastin fibers, vascular smooth muscle cell apoptosis, calcifications, inflammation and fibrosis, endothelial dysfunction)[56–67] and wall thickness and/or radius, i.e., arterial remodeling.[68] The latter is the response to changes of mechanical forces, such as shear stress acting on the endothelium and cyclic circumferential strain affecting the endothelium and smooth muscle cells.[68–71]

Arterial remodeling characteristics depend largely on the nature of hemodynamic stimuli. According to Laplace's law, arterial tensile stress (σ) is proportional to transmural pressure (P) and radius (r), and inversely proportional to wall thickness (h) ($\sigma = Pr/h$). In response to increased blood pressure or arterial radius, vessel wall thickening and higher wall-to-lumen ratio[68,69] maintain tensile stress. Blood flow alterations result in shear stress (τ) changes directly proportional to blood flow (Q) and blood viscosity (η), and inversely proportional to vessel radius (r) ($\tau = Q\eta/\pi r^3$). In response to blood flow changes, shear stress is maintained by changing arterial cross-sectional lumen area.[70,71]

MEASUREMENT OF ARTERIAL STIFFNESS

Because the methodological issues concerning the measurement of various stiffness indices and their clinical applications were published recently and reviewed in detail,[72–76] herein we briefly mention only the most relevant ones for clinical and pathophysiological studies. There are two main techniques to measure arterial stiffness: directly or to estimate it indirectly from circulation models. The main characteristics of the devices used to measure arterial rigidity are summarized in Table 1.

Direct measurement of arterial stiffness

PWV is the most widely used technique that Bramwell and Hill[77] introduced to physiology in 1929. Briefly, a pressure wave's propagation speed in a solid is proportional to its stiffness. If expressed through the elastic modulus (E_{inc}), PWV can be expressed as $PWV = K \times E^{0.5}$, where K reflects tissue density. Thus, when measuring the pressure wave at different sites along an arterial segment or along the arterial tree (dL), the distal wave is recorded later (dt) than the proximal one and PWV = dL/dt. Waveform landmarks that are in concert from one side to another have to be used; the foot of the pressure wave is widely used because it is more clearly identified on all sites.

Although PWV can be measured on any artery or between any arterial sites, only carotid-to-femoral PWV has been shown to have predictive value for morbidity and mortality.[14,21,28] It represents stiffness of the aorta and iliofemoral axes. The several commercial devices available differ according to the type of signal (pressure, distension, flow) or whether they simultaneously record both sites or use the electrocardiogram for synchronization. When a high-fidelity pressure transducer is used, they may allow pressure wave analysis and wave reflection assessment. PWV reference values determined in a

Table 1 | Techniques to estimate arterial stiffness

Techniques	Manufacturer	Signal	Probe	Remarks
Direct PWV measurement				
Complior	Alam Medical, Vincennes, France	Pressure	Standard	Simultaneous
Sphygmocor	AtCor Medical, Sydney, Australia	Pressure	High fidelity	ECG triggered
PulsePen	Diatechne, Milan, Italy	Pressure	High fidelity	ECG triggered
PulseTrace	Micromedical, Chatham Maritime, UK	Flow	Doppler	ECG triggered
Vicorder	Skidmore Medical, Bristol, UK	Pressure	Cuff	Simultaneous
Ankle brachial PWV				
Omron VP-1000	Omron Medical, Kyoto, Japan	Plethysmography	Cuff	Simultaneous
Other				
Q-KD	Novacor, Rueil Malmaison, France	Korotkov sounds	Cuff	ECG triggered
Echotracking techniques				
Artlab System	Esaote, Genoa, Italy	128 Lines		Online
E-Traking	Aloka, Tokyo, Japan	4 Lines		Online
HDI-lab	Philips, Eindhoven, Netherlands	NA		Offline
Indirect techniques				
CVProfilor	HD (Hypertension Diagnostics), Eagan, MN	Pressure	Cuff	
Arteriograph	Medexperts, Budapest, Hungary	Pressure	Cuff	Suprasystolic inflation
Mobilograph	IEM Healthcare, Stolberg, Germany	Pressure	Cuff	

Abbreviations: ECG, electrocardiogram; PWV, pulse wave velocity.

very large population are now available, and measurement standardization based on those values was recently proposed.[78]

Distance measurement and identification of the foot of the wave are important issues. To have realistic PWV values, the use of intersecting tangents to measure transit time (dt) of the foot of the wave and carotid-to-femoral distance (dL) is preferred; PWV is then calculated as $PWV = 0.8 \times dL/dt$.[78] Techniques derived from PWV, e.g., the brachial ankle PWV, might be of interest, but because the wave is propagating simultaneously in the arm and the aorta much of the aorta is simply ignored by this parameter, which limits its usefulness. The quantum key distribution technique measures the time interval between the electrocardiogram Q wave and the first Korotkov sound during ambulatory blood pressure monitoring.[72,74] This technique provides an estimate of stiffness partly dependent on heart rate because of variable electromechanical coupling time.

It is also possible to directly measure arterial dimension changes during the cardiac cycle and link them to local pulse pressure changes. This approach is straightforward and provides the pressure–diameter relationship, the stress–strain relationship if thickness is also measured, and, thus, yields stiffness indexes at any given blood pressure level. These techniques are based on high-precision vascular echotracking or magnetic resonance imaging and applanation tonometry.[72,74–76] Measurement of stiffness using the pressure–diameter relationship has not been validated as much as PWV, in terms of prediction of cardiovascular events. Nevertheless, measurement of local stiffness remains useful for clinical research.

Indirect estimation of arterial stiffness

These techniques rely on simplified circulation models. The most widely used is the Windkessel model.[5,23] The diastolic blood pressure decay is exponential, and the constant of this exponential modeling is proportional to rigidity. This model can be made more complex by using two exponential functions: one for large arteries (C1) and the other for small arteries (C2).[79,80] To date, only one epidemiological study validating this technique has been published,[80] and this has been conducted only for small-artery compliance.

Another indirect technique, aortic characteristic impedance, requires flow and pressure measurement at the aortic root.[5,23,29] Characteristic impedance is the minimal impedance for higher frequencies of pressure and flow harmonics. It is proportional to PWV. This technique is rarely used alone, as it is hampered by the difficulty of obtaining reliable noninvasive data for aortic flow and pressure. On the list are also rigidity estimates derived from blood pressure measurement, e.g., ambulatory blood pressure monitoring–derived ambulatory arterial stiffness index (1/slope of the systolic blood-pressure–diastolic blood-pressure relationship) or crude brachial pulse pressure.[81] Although these values reflect arterial stiffness, they provide very different information, which might eventually make them useful for patient evaluation, but clearly are not surrogates for direct artery stiffness measurements.

ARTERIAL STIFFNESS IN VARIOUS CLINICAL CONDITIONS

Numerous publications and several reviews[58,82–84] reported the various pathophysiological conditions associated with increased arterial stiffness and wave reflections. Apart from the dominant effect of aging,[78,84–86] they include the following: physiological conditions, such as low birth weight,[86] menopausal status,[87] and/or lack of physical activity;[88] genetic background, such as family history of hypertension and diabetes,[89,90] and/or myocardial infarction[90] and genetic polymorphisms;[91] cardiovascular risk factors, such as obesity,[92] smoking,[93] hypertension,[94,95] hypercholesterolemia,[96,97]

impaired glucose tolerance,[98,99] metabolic syndrome,[92,100] type 1 or 2 diabetes,[100] hyperhomocysteinemia,[100] and/or high C-reactive protein (CRP) level;[101] and cardiovascular diseases, for example, coronary heart disease,[20] congestive heart failure,[102] and fatal stroke.[21] The influence of CKD or ESRD[11,13,103,104] is detailed below. The contributions of these different factors to arterial stiffness and wave reflections were subjected to multivariate analyses: when evaluating the degree of arterial stiffness, the major parameters to be considered are age and blood pressure, and, to a lesser extent, sex and classical cardiovascular risk factors.

Pertinently, primarily non-cardiovascular diseases, such as rheumatoid arthritis,[105,106] systemic vasculitides,[59] and systemic lupus erythematosus,[107] are associated with increased aortic rigidity, underscoring the role of inflammation in the stiffening of large arteries. The inflammation process, either acute during *Salmonella typhi* vaccination[60] or chronic during rheumatoid arthritis[59,60] or systemic lupus erythematosus,[107] was reported to rigidify the large arteries. This stiffening may occur through various mechanisms, including endothelial dysfunction, cell release of any number of inducible matrix metalloproteinases (including MMP-9), medial calcifications, modified proteoglycan composition and hydration state, and/or cell infiltration around the vasa vasorum leading to vessel ischemia.[60,61] The association of arterial stiffening and inflammation in essential hypertension was demonstrated through the relationships between arterial stiffness and either tumor necrosis factor-alpha (TNFα), interleukin-6, or highly sensitive CRP (hs-CRP).[101,108,109] The primary proinflammatory cytokines, TNFα, and interleukin-6, are the main inducers of hepatic hs-CRP synthesis. Interleukin-6 and hs-CRP are independent predictors of increased risk of coronary artery disease. Interleukin-6 and TNFα are also independent risk factors for high blood pressure in apparently healthy subjects. In untreated patients with essential hypertension, aortic stiffness, assessed through carotid-to-femoral PWV, was significantly associated with hs-CRP and interleukin-6.[108] According to the REASON study, baseline hs-CRP was an independent predictor of carotid-to-femoral PWV, central augmentation index, and lower central pulse pressure after antihypertensive treatment.[109]

ARTERIAL REMODELING AND STIFFNESS IN CKD STAGES 2–5

The risk of developing cardiovascular disease increases with kidney–disease progression and is already observed in patients with isolated proteinuria or slightly reduced glomerular filtration rate (GFR).[110–112] Patients with CKD stage 4 are more likely to die than to progress to ESRD, and most of their deaths are due to cardiovascular diseases.[112,113] CKD is characterized by a high prevalence of conventional (hypertension, diabetes, dyslipidemia) and nonconventional (oxidative stress, inflammation, anemia, mineral-metabolism disturbance(s)) cardiovascular risk factors.[114–116] Exposing the arteries to this environment might influence arterial structure and induce arterial remodeling and stiffening (Figure 4a and b).

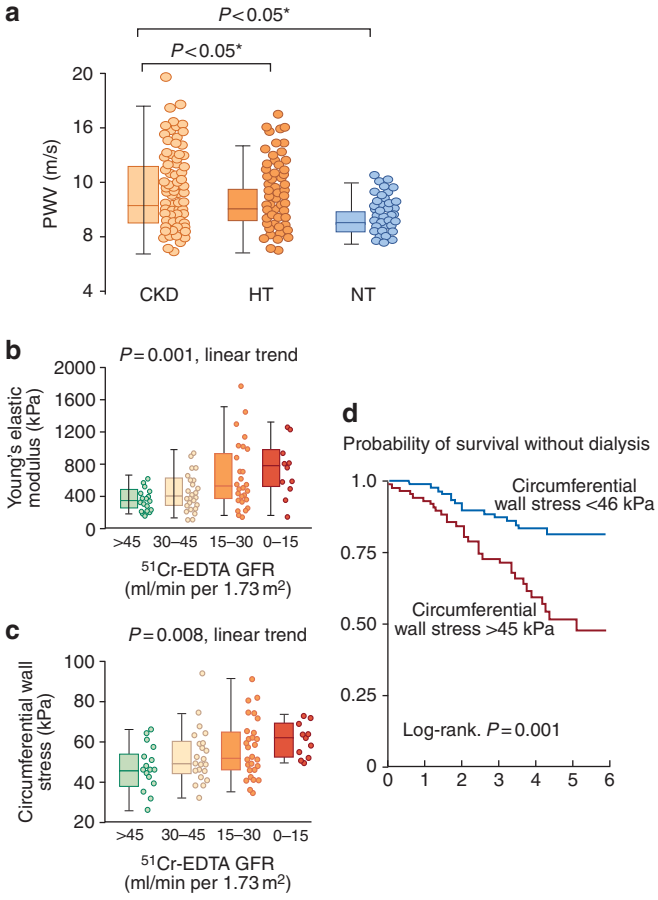

Figure 4 | Arterial stiffness phenotypes in chronic kidney disease (CKD) stages 2–5 patients compared with normotensive (NT) and hypertensive (HT) controls. (**a**) Aortic pulse wave velocity (PWV), (**b**) Young's elastic modulus, (**c**) circumferential stress, and (**d**) probability of survival without dialysis according to circumferential wall stress.[104,118] Cr-EDTA, chromium-labeled ethylenediaminetetraacetic acid; GFR, glomerular filtration rate.

Arterial remodeling is already observed in early-stage CKD and its progression.[104] Compared with normotensive and hypertensive controls, patients with CKD stages 2–5 had significantly larger internal carotid artery diameters but comparable intima–media thicknesses, resulting in significantly increased circumferential wall stress (Figure 4b). Their carotid elastic modulus increased with CKD progression but did not differ from that of blood pressure–matched hypertensive controls. In contrast to carotid stiffness, their carotid-to-femoral (aortic) PWV was significantly higher than that of hypertensive and normotensive controls, suggesting that the rigidity of the two vessels could progress differently in this population (Figure 4a).[104]

In CKD, wall thickening did not compensate for the increased lumen diameter, resulting in heightened circumferential wall stress, indicating pressure-unadapted large artery remodeling in CKD (Figure 4b). In contrast to observations made in non-uremic atherosclerosis patients,[117] a recent study showed that carotid intima–media thickness declined

during worsening CKD.[118] In that cohort, circumferential wall stress was the only arterial parameter independently associated with CKD deterioration and ESRD[118] (Figure 4). Because of their antiproliferative properties, renin–angiotensin system blockers, often prescribed to CKD patients, could have a role in the thickening defect.[119,120] Excessive vascular smooth muscle cell apoptosis is another hypothesis. Shroff *et al.*[121] found apoptosis-related rarification of vascular smooth muscle cells in children with ESRD compared with patients without CKD. Finally, enhanced extracellular matrix turnover with high MMP activity could also contribute to the observed phenotype. MMPs are involved in flow-induced outward vascular remodeling[122] and several aspects of cardiovascular remodeling, e.g., left ventricular hypertrophy, atherosclerosis, and/or aortic aneurysm.[123–125] Several studies on CKD patients showed serum-level variations of MMPs and their inhibitors.[126,127]

Arterial enlargement, arterial stiffening, and increased circumferential wall stress occurred in parallel with GFR decline, but their relative importance is more complex.[118] Compared with hypertensive patients and healthy subjects, CKD patients had greater aortic stiffness even after adjustment for age and blood pressure.[104,118,128–132] However, within CKD populations, conflicting results were published as to whether aortic stiffness was associated with CKD severity. Cross-sectional investigations, including the recent CRIC study that included 2,564 CKD patients, demonstrated an independent association between aortic stiffness and CKD stages.[132,133] Lilitkarntakul *et al.*[134] recently reported that CKD patients' blood pressure, not renal function, was the major determinant of arterial stiffness. We and others found no association between aortic rigidity and CKD stages within the CKD population.[118,135] However, in both those studies, carotid stiffness was independently associated with CKD stages, thereby suggesting that carotid and aortic hardening could progress differently in this population.

In addition, the recent publication of the arterial ancillary study on the NephroTest cohort provided findings showing that aortic stiffness was stable over time, whereas carotid rigidity increased significantly during follow-up ($+0.28 \pm 0.05$ m/s).[122] Notably, in that cohort, aortic stiffness was not associated with CKD progression.[118] The absence of such an association was also observed in another CKD cohort.[136] In the latter, only the baseline phosphate level was independently associated with CKD worsening. In contrast, Ford *et al.*[137] found aortic stiffness to be associated with deteriorating CKD. However, in their study, the correlations were weak and CKD progression was based on estimated GFR, whereas in the NephroTest cohort it was measured with ^{51}Cr-EDTA (chromium-labeled ethylenediaminetetraacetic acid) clearance.[118] Very few data on carotid stiffness are available. We recently reported that carotid stiffness was not independently associated with CKD deterioration.[118] Further investigations are needed to elucidate the role of arterial rigidity in advancing CKD and the differential arterial stiffness progression within the different arterial segments during CKD.

ARTERIAL REMODELING AND STIFFNESS IN ESRD (CKD 5D)

Atherosclerosis is highly prevalent in ESRD patients.[1–3,138–141] The high atherosclerosis incidence in ESRD patients on replacement therapy led to the hypothesis that atherogenesis is accelerated in chronically hemodialyzed patients.[1] Because many ESRD patients frequently have severe vascular lesions before initiating replacement therapy, and, in many, generalized atherosclerosis can be the primary cause of renal failure, it remains a matter of debate whether atherogenesis is accelerated. Nevertheless, the features of ESRD patients' atherosclerotic plaques, with a higher prevalence of calcified plaques, are different from those of control general populations.[140–142]

Early vascular aging

The most characteristic arterial change observed in ESRD patients is the so-called 'accelerated arterial aging', typified by outward remodeling and arterial stiffening[11,12,142–149] (Figures 5 and 6). Their age-related hardening is much more pronounced in the aorta and central arteries than in muscular-type peripheral arteries[11,28,143,150] responsible for accelerated reduction of the impedance mismatch and

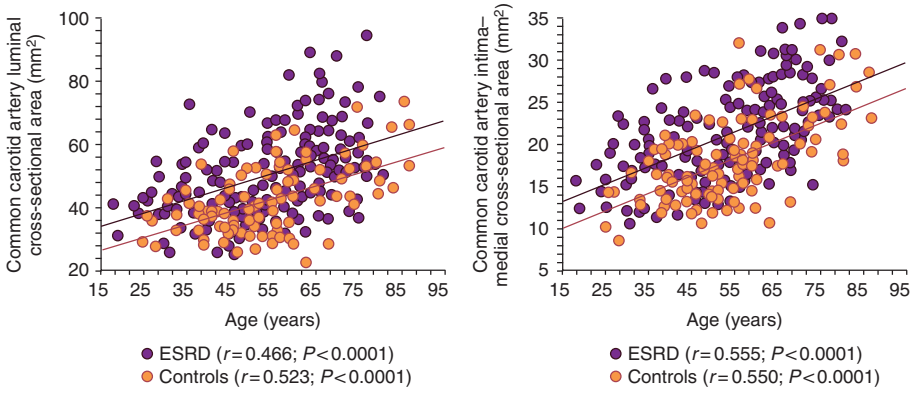

Figure 5 | Correlations between common artery diameter or intima–media thickness and age of end-stage renal disease (ESRD) patients and controls. Adapted From Pannier *et al.*[28,143]

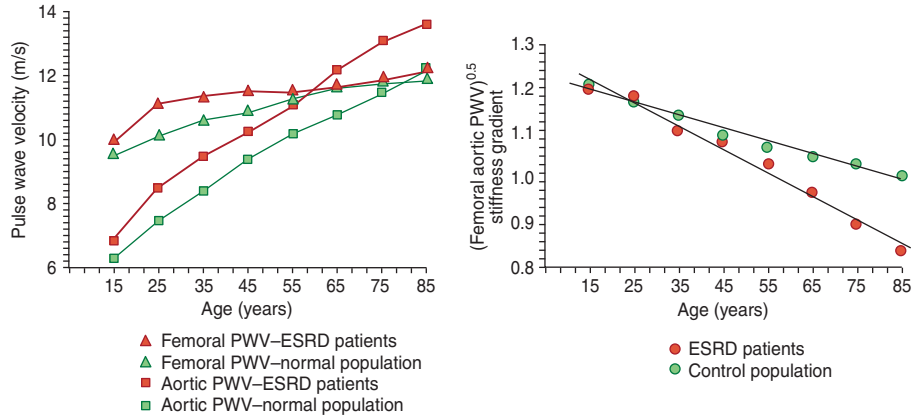

Figure 6 | Aortic and femoral pulse wave velocity (PWV) as a function of age of end-stage renal disease (ESRD) patients and controls (mean; left panel). Femoral/aortic PWV ratio (stiffness gradient) in ESRD patients and controls (right panel). Adapted from Pannier *et al.*[28,143]

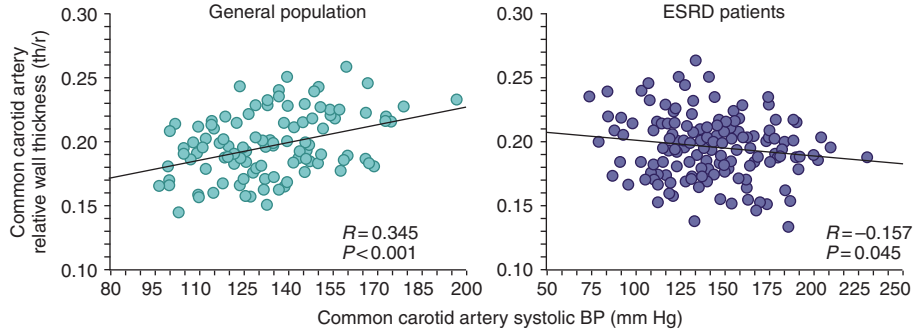

Figure 7 | Correlations between common carotid artery systolic blood pressure (BP) and common carotid artery relative wall thickness (intima–media thickness/radius ratio (th/r)) in controls and end-stage renal disease (ESRD) patients. Adapted from Pannier *et al.*[143]

diminished buffering capacity to lower pulsatile pressure transmission to the peripheral microcirculation (Figure 3). Normal arterial aging is characterized by arterial enlargement, wall thickening, and stiffening.[22,56] ESRD patients' arterial remodeling is characterized by increased arterial diameters and intima–media thickness, and wall-to-lumen ratio similar to control subjects.[11,143] Nevertheless, as in earlier CKD stages, the hypertrophic response is 'inadequate'. According to Laplace's law, when blood pressure increases, and regardless of the internal radius, the wall-to-lumen ratio (relative wall thickness) should increase to normalize circumferential tensile stress. In the general population, this increase is characterized by a positive relationship between systolic blood pressure and arterial wall-to-lumen ratio (Figure 7). This relationship is lost in ESRD patients whose wall-to-lumen ratio tends to decline with pressure, leading to inadequate hypertrophy and abnormally increased circumferential tensile stress. The high tensile stress and limited arterial capacity to hypertrophy is a pathophysiological continuum observed from CKD stages 2–5 to CKD 5D. In ESRD patients, the arteries, including the brachial artery without the arteriovenous fistula, are enlarged, usually with similar blood flows.[151] These changes (enlarged diameter with similar flows, i.e., lower flow velocity) result in significantly lower shear stress, because of low shear rate and anemia-associated low whole-blood viscosity.[151] Because physiological shear stress promotes endothelial cell survival and quiescence,[152,153] the lower shear stress in ESRD patients is associated with high circulating levels of endothelial microparticles, increased arterial rigidity, and diminished endothelial flow–mediated dilation.[63,154]

Arterial stiffness is 'pressure dependent' and, in essential hypertensive patients, the diminished arterial distensibility is, in part, due to higher distending blood pressure. When adjusted for blood pressure differences (i.e., under isobaric conditions), the arterial distensibility and/or elastic modulus of essential hypertensive subjects are more distensible than (in muscular conduit arteries) or similar (in elastic capacitive arteries) to those observed in normotensive controls.[155–158] This concept differs from the observations made in CKD patients or experimental models, in which arterial stiffness increased under isobaric conditions.[159] In CKD and ESRD, hardening is associated with alterations of the intrinsic elastic properties of arterial walls (increased E_{inc}), namely fibroelastic intimal thickening, calcification of elastic lamellae, elastinolysis and inflammation, increased collagen content and collagen

cross-linking, apoptosis, and rarified numbers of vascular smooth muscle cells.[121,159–162] These arterial wall changes are influenced not only by nonspecific factors, such as age, genetics, hypertension, diabetes, lipid abnormalities, inflammation, and/or common atherosclerosis, but also by parameter(s) associated with the presence of uremia *per se*. Mineral and bone disorders are the most frequently observed factors associated with arterial remodeling and functional alterations in CKD and ESRD.[67,162–166] In hemodialyzed patients, arterial stiffness was associated with arterial calcifications[67,164–166] and it worsened with the increasing calcifications.[131]

Calcifications

Arterial calcifications are common CKD and ESRD complications.[67,167,168] The pathogenesis of calcification is multifactorial, implicating factors inducing and opposing it, with plasma constituents maintaining minerals in solution and inhibiting their deposition in tissues.[169–174] The results of several recent studies showed that low serum levels of the soluble calcification inhibitor fetuin-A were an independent predictor of aortic and carotid stiffness.[172–175] Studies on ESRD patients in general populations showed strong associations between vitamin D deficiency and increased arterial stiffness, as well as deficient endothelial function, respectively.[176–179] Clinical studies demonstrated that vitamin D supplementation reduced MMP activity,[180] which is usually associated with high aortic PWV.[181] Vitamin D supplementation also had beneficial effects on the elastic properties of vessel walls.[182] In ESRD, the mineral-metabolism disturbances are associated with uremic bone disease. An inverse relationship of arterial calcification and stiffness with bone density or bone turnover was observed in CKD and ESRD patients.[183–187]

Response to intervention

Although aortic stiffness provides good prognostic information, unequivocal evidence is still required for some therapies proposed to attenuate arterial stiffness in CKD patients. Such an effect should reflect a real diminution of arterial wall rigidity, independent of other risk factor corrections, e.g., blood pressure, lipid disorders, and others. In general populations, many therapeutic strategies to prevent arterial stiffness have been proposed, including lifestyle modifications or pharmacological approaches.[58] Arterial hardening is pressure dependent and blood pressure reduction should normally contain rigidification. Guérin *et al.*[17] provided the first evidence that, in ESRD patients, aortic PWV insensitivity to blood pressure reduction was an independent predictor of mortality. Experimental and clinical studies showed that pharmacological inhibition of the renin–angiotensin–aldosterone system was the most efficient.[17,188,189] Advanced glycation end-product formation is associated with arterial stiffness, and advanced glycation end-product cross-link braker has been shown to reduce arterial stiffness in elderly subjects[190] and improve endothelial function in patients with isolated hypertension,[191] but was not tested in CKD and ESRD patients.

The effect of renal transplantation on stiffness remains contradictory: some observations suggested an attenuation after living donor transplantation[192] or short-term, but not long-term, improvement after cadaveric engraftment.[193] Arterial stiffness usually stays high in kidney transplant recipients, associated with incomplete GFR restoration and impaired renal allograft function.[194,195] The long-term aortic stiffness seen in cadaveric kidney transplant recipients seems to be significantly influenced by donor age: less rigidity in recipients of young kidneys and further deterioration in those receiving older kidneys.[196] A large prospective study is still needed to define the effect of kidney transplantation on vascular stiffening.

In recent years, many studies emphasized the role of arterial stiffness in the development of cardiovascular diseases, and it was shown that arterial rigidity is associated with increased cardiovascular mortality and morbidity. Arterial rigidity is closely associated with vascular aging. Premature vascular aging and arterial stiffening are observed with CKD progression and in ESRD. This accelerated aging is associated with outward remodeling of large vessels, characterized by enlarged arterial radius, incompletely compensated for by artery wall hypertrophy. Arterial hardening in CKD and ESRD patients is of multifactorial origin, with extensive arterial calcifications representing a major covariate. With aging, the stiffening is more pronounced in the aorta than peripheral conduit arteries, leading to disappearance or inversion of the arterial stiffness gradient with diminished protection of the microcirculation against high-pressure transmission. Various non-pharmacological or pharmacological interventions can modestly slow arterial stiffness, but treatments able to prevent stiffness mainly include antihypertensive drugs.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This work was supported by G.E.P.I.R (Groupe d'Étude de la Physiopathologie de l'Insuffisance Rénale) and INSERM U970.

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